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Chapter 6

AEROSOL FORMULATION, GENERATION, AND DELIVERY USING NONMETERED SYSTEMS

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I. METERED VS. NONMETERED SYSTEMS

Devices which can be used to generate inhalation aerosols fall into two main categories: those which purport to meter the drug dose provided to the patient and those which do not. Because the formulation of metered dose inhalers or MDIs presents the pharmaceutical scientist with some unique challenges, these devices are described separately in another chapter. The present chapter attempts to come to grips with the principles of operation of continuous aerosol generators and their use in the treatment of human disease. These devices, of which nebulizers are the most common example, are used widely by pharmacologists involved with drug testing in animals and are increasingly seen as a useful adjunct to MDI therapy in humans. Despite the implication in the chapter title that nebulizers provide an unknown dose, they can be used conveniently by researchers who seek to establish the dosimetry of compounds delivered to the lungs. This step is a necessity in the development phase for a new drug entity and should be performed prior to the formulation and design of metered dose units. While the majority of this chapter is concerned with the use of continuous aerosol generators to administer drugs in a therapeutic setting, two sections (II.C and V.C) address the subject of assigning a value for "dose to the lung" applicable to a drug development protocol.

Some of the advantages and disadvantages of nonmetered systems such as portable nebulizers are listed in Table 1. In view of the fact that aerosols are presently inhaled mostly by breathing-impaired patients, the predominant factor dictating the use of a nebulizer over an MDI is patient preference. Nebulizers offer the possibility of tidal inhalation and exhalation (as opposed to deep inhalation and breath-hold, phased with actuation for optimal MDI usage). However, in view of the fact that some new compounds may be administered to lung-normal patients (for systemic delivery perhaps), this factor is drug and disease specific. From a technological point of view, the possibility of administering much larger doses by employing continuous aerosol inhalation is the nebulizer's most appealing advantage. Disadvantages, on the other hand, are many; the level of patient education is critical if hygiene is to be maintained and, because of the complexity associated with these devices, much of the control remains in the hands of the patient. The wide variety of available devices and their different specifications makes misuse a likely occurence.

II. ESTIMATING DOSIMETRY

Only a basic understanding of the factors affecting aerosol deposition in the lung is necessary in order to realize that neither continuous generators nor so-called "metered dose inhalers" really control the drug dose reaching the airways of the lung. It is true that the MDI limits the amount a patient can inhale from a single actuation of the inhaler, but in neither this case, nor that of the nebulizer, will all of the aerosolized material reach and deposit in the lung. While it is not the intention to review deposition in detail (see Chapter 1), the importance of defining dosimetry in terms of drug mass requires that a simple mass-based deposition model be presented here as a precursor to later arguments to be used in this and the next chapter.

A. STABLE AEROSOLS INHALED BY NORMAL HUMANS

When discussing the different categories of generation and delivery device, it is helpful to keep a simple model of aerosol deposition in mind. Aerosol size distribution is the single most important variable in defining the site of droplet or particle deposition in the patient; in short, it will determine whether drug targeting succeeds or fails. From a pharmaceutical point of view, the most important parameter is usually the mass median aerodynamic diameter (MMAD) of an aerosol. This is the aerodynamic diameter above and below which 50% of the mass resides. Aerodynamic diameter is the diameter of a unit density sphere which behaves in air in the same way as the droplet or particle in question. In the frequent event that MMAD is determined by

TABLE 1
Advantages and Disadvantages of Nonmetered Aerosol Delivery Devices

Advantages	Disadvantages
1. Large respirable dose	1. Complexity
2. Patient preference[a]	2. Expense and portability
3. Water is usually the solvent[b]	3. Hygiene maintainence
4. Patient coordination is not usually a problem	4. Devices and techniques are nonstandardized

[a] In the home; in public places, smaller devices like MDIs are usually preferred.
[b] Propellant and excipient toxicity is not an issue.

fractionating the aerosol according to droplet size and then analyzing drug content in each of the fractions, then the term reflects the size above and below which 50% of the drug mass resides.[1] Because the concentration of drug may be different in small and large droplets, this is not necessarily the same as the MMAD of the aerosol itself. Nevertheless, it is this drug MMAD which matters here because this will define how the drug mass will deposit in the lung.[2] It is important when reading the literature to realize that the mass median diameter is often about three to four times larger than either the count or number mean or median diameters.[3] The number median, for example, is the diameter above and below which 50% of the number of droplets resides. The latter value is smaller than the MMAD because a single 10 μm sphere has 1000 times the mass of one with a diameter of 1 μm. Articles in the medical literature and device manufacturers frequently state count mean diameters to describe the output of different devices which make the aerosols sound much better for inhalation than they really are.[4] Diameters other than aerodynamic are sometimes also quoted. The difference between actual and aerodynamic diameters, d_{ae}, which are related through the density and shape of the particle or droplet, is given for spheres with diameters greater than ≈1 μm by

$$d_{ae} = (\text{actual diameter}) \cdot (\text{density})^{1/2} \quad (1)$$

where density is expressed in gcm^{-3}. This relationship is less important for aqueous aerosols than it is for aerosolized pharmaceutical powders where densities are often in the range of 1 to 2 gcm^{-3}.[5] Readers should review a simple text on particle size analysis[3] in order to clarify their understanding of these points. Provided an aerosol is log-normally distributed and the geometric standard deviation is known, it is possible to relate the different mean and median diameters analytically. Even so, because therapeutic aerosols often deviate from log-normality and sometimes display polymodal distributions, it is better to measure the MMAD itself rather than try to calculate it from some other value.[6]

Different aerosol size distributions may be expected to deposit preferentially in different regions of the respiratory tract. Aerosols inhaled through the nose have different deposition patterns to those inhaled orally.[7] In Figure 1, oral inhalation by normal subjects is assumed because this is the more frequent mode of inhalation. Fractional deposition (in terms of particle or droplet mass) is shown for monodisperse, stable aerosols. The data in support of Figure 1 are derived from human exposure to radiolabeled dust aerosols with subjects inhaling and exhaling tidally.[7,8] If the horizontal axis on Figure 1 were labeled "mass median aerodynamic diameter" so that polydisperse aerosols were considered,[9] the curves indicating deposition in the lung may be reduced in height, indicating less efficient deposition, but the maxima would remain at the same diameters.[10] In normal subjects, deposition in the pulmonary or alveolar compartment is optimal for aerosols with aerodynamic diameters around 2 to 3 μm provided inhalation is slow (20 to 30 l/min).[7,11] Maximum deposition in the tracheobronchial regions occurs with slightly

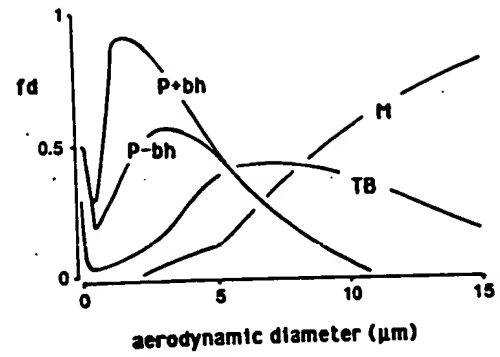

FIGURE 1. Simulated fractional mass deposition, fd, vs. aerodynamic diameter (μm) in oropharynx or mouth (M), tracheobronchial region (TB), and pulmonary region with (P + bh) and without breath-hold (P – bh). Deposition is for stable monodisperse aerosols inhaled by normal humans breathing tidally with inspiratory flow rates ≈22 l/min. Polydisperse aerosols produce similar curves with lower maxima when mass median aerodynamic diameter is plotted on the horizontal axis. (Reproduced with permission of the American Pharmaceutical Association.)

larger particles, although mucociliary clearance can remove material quite quickly from this region (Chapter 6).

B. BREATHING PATTERN AND DISEASE

The curve maxima in Figure 1 shift on both axes if the breathing pattern is changed. With faster inhalation, smaller aerosols usually deposit higher in the respiratory tract (tracheobronchial deposition is enhanced) than would be the case if inhalation were slow. In part this is due to increased turbulence. The tracheobronchial or conducting airways extend down to the terminal bronchioles.[9] Constriction of the tracheobronchial airways is responsible for most of the breathing difficulty in reversible asthma. Unlike the pulmonary region, these airways have smooth muscle in their walls. It is obvious that aerosol deposition in an asthmatic individual will be different from that in a normal subject. Partly due to turbulence in constricted airways but also because the aerosol cannot penetrate well into poorly ventilated areas, deposition tends to occur more centrally in patients than it does in normal subjects.[12] Also, intersubject variations in deposition are much larger in the diseased population. This variability in aerosol deposition, which the pathophysiology of asthma creates,[12] obliterates many of the finer differences resulting from aerosol size changes and breathing pattern. Even so, the trends shown in Figure 1 remain broadly true. Aerosol particles with larger aerodynamic diameters have an increased tendency to collide with surfaces in their paths and separate by impaction in the upper airways. Smaller particles (which form more stable aerosols) tend to separate largely by sedimentation in the small, peripheral airways provided the airflow takes them there. The upper curve in Figure 1 shows an estimate of the increased deposition in the lung periphery resulting from breath-holding after inhalation.[11] If small particles (≈2 μm; Figure 1) do not reach the periphery, where the sedimentation distances become small enough for them to deposit during a breath-holding pause, then they are more likely to be exhaled.[1,13] In the bronchoconstricted asthmatic, when airway narrowing is substantial, some small enhancement in deposition due to settling may be expected in the upper airways as a result of breath-holding.

C. PRINCIPLES OF DOSE ESTIMATION

Presumably, the drug formulator and product designer wish to deliver a known dose more or less reliably to the lungs of a patient. If we assume at this stage that it is possible to generate several tidal volumes of homogeneously distributed aerosol and make this available at the subject's mouth, in principle it is then possible for the formulator to estimate the dose administered to the lungs. Several basics should be standardized and have known values. These are

1. Drug concentration in air
2. Aerosol size distribution (drug MMAD and a measure of polydispersity)
3. The subject's breathing pattern (rate and frequency of inspiration, duration of breath-hold, and inhaled volume)

Then, let us assume that a well-trained, "lung-normal" subject inhales at a known rate, say 20 to 30 l/min, and breath-holds for a chosen interval. Assume further that he or she inhales a tidal volume of aerosol equal to 3 l on 4 separate inhalations. If the aerosol size is known, then it is usually possible to choose an appropriate deposition model and assign a value to mass fractional deposition, fd (Figure 1). This may be in the whole lung (TB + P; Figure 1) or a portion of it, as described in an earlier chapter, whichever is considered to be most important. The product of the aerosol concentration and inhaled volume then provides an estimate of the drug mass inhaled which, when multiplied by fd, gives the estimated dose deposited. While some of the deficiencies of this approach are discussed later in Section V.C, it is apparent that the aerosol formulator and device designer must work closely together *to produce a combination which delivers drug in aerosolized form with an appropriate concentration and particle size distribution so as to optimize its mass deposition in the respiratory tract*. The aerosol concentration and size distribution which matters is the one which the patient sees at his or her oro- or nasopharynx, and is not necessarily the one which was determined perhaps 1 m of tubing before reaching the patient. Although it is difficult to achieve, the ideal aerosol should be presented to the patient as a stationary, stable cloud of particles or droplets suspended in air.

III. DYNAMICS OF INHALATION AEROSOLS

An understanding of three important phenomena which affect aerosol size and concentration are required prior to explaining the performance characteristics of different devices. An understanding of particle or droplet impaction, sedimentation, and solvent evaporation or condensation kinetics is essential to the design of successful administration systems. These three phenomena (impaction, sedimentation, and the size changes induced by evaporation or condensation) stand out from others in aerosol physics (thermophoresis, photophoresis, and particle diffusion, for example) as being the primary mechanisms by which aerosolized medicaments separate and/or change their particle size distributions most rapidly within delivery systems. Each topic is described briefly in turn.

A. DROPLET OR PARTICLE IMPACTION

Aerosol segregation on the basis of the inertial properties of the dispersed phase is important not only to explain deposition in the upper airways (Chapter 1), but also to understand some of the principles by which inhalation devices function and, in some cases, fail to function. It is necessary to gain a simple understanding of the process (which is also used as the principle of operation for cascade impactors) sufficient to be able to say when droplet impaction is or is not likely to occur. Figure 2 is a schematic showing aerosol passage within a circular tube of internal diameter, W. The large droplet is shown leaving the airflow and impacting while the smaller one deviates with the airflow. In order to simplify the theory, the distance from the end of the tube

TABLE 2
Sedimentation Velocities of Unit Density Spheres in Dry Air at 20°C and 1 atm Pressure

Aerodynamic diameter (μm)	Sedimentation velocity (cm/s)
2.0	0.013
4.0	0.050
6.0	0.111
8.0	0.197
10.0	0.306
20.0	1.212

estimated quite simply from the ratio of distance settled in the residence time to the internal diameter of the tubing. Although these arguments neglect to account for turbulent mixing, they can be extended to their logical conclusions which are frequently found in practice to be correct. There are three main results of passing polydispersed aerosols in our size range of interest (Figure 1) along tubes. The segregation induced by the sedimentation process ensures that the aerosol flowing from the tubing outlet has (1) decreased concentration, (2) a smaller median diameter, and (3) decreased "polydispersity". The relative magnitude of all these segregation effects becomes smaller as the aerosol droplet or particle size is reduced at the inlet to the tube because the aerosol becomes "more stable" and is less likely to sediment quickly. The "polydispersity" of the aerosol distribution refers to the magnitude of the spread of the particle size distribution. It is frequently characterized numerically as the geometric standard deviation (GSD) of log-normally distributed aerosols.[3] Some of these effects are shown in our work designed to determine drug absorption kinetics after characterized aerosol administration to dogs.[14,15] As they were generated, the aerosols of three median sizes were all significantly polydispersed (GSD ≈ 2). After passage along the tubes required for administration by positive pressure ventilation, however, segregation caused the larger aerosols (3.5 and 4 μm MMAD) to tend toward monodispersity (GSD = 1.3). This effect was much less for the smallest aerosol (1.0 μm MMAD) which was administered after passage through the same apparatus, with a GSD equal to 1.6.[15]

C. EVAPORATION AND CONDENSATION

Therapeutic aerosols are unstable in two major respects. First, they contain droplets or particles which are too large to stay in suspension for long. Second, they contain volatile or hygroscopic materials which cause aerosol size changes to occur as a function of time, temperature, aerosol dilution, and droplet or particle content. The thermodynamics and kinetics of this latter subject are too complex to consider in detail here, even when single particles or droplets are considered. In simple terms, and as far as therapeutic aerosols are concerned, two questions are of importance:

1. How *fast* can evaporation or condensation alter the particle size distribution of an aerosol?
2. How *much* can they change the size distribution (if they occur fast enough)?

The enormous surface:volume ratio presented by typical medicinal aerosols requires that we think of water as a volatile material and thus, a reasonable answer to the first question is "fast enough to worry about". The calculated lifetime of a 10-μm water droplet at 25°C and 80% relative humidity is only ≈0.6 s^{16} and a breath of aerosol usually takes several seconds to inhale.[1] Furthermore, and with obvious relevance to MDIs, some of the solvents and propellants used

in therapeutic aerosols are more volatile than water. Thus, as a rule of thumb, we can often assume that aerosols adjust their size distributions extremely quickly. To answer the second question, droplets will grow or shrink until their solvent vapor pressures are in equilibrium with the environment. Different droplet "environments" may display a wide range of temperatures but rarely contain fluorocarbon or ethanol vapors in significant concentrations. While ingredients like these *should* be lost rapidly and completely, we will see the complexity of the subject in the following chapter, when we observe that inadequate heat transfer to supercooled propellant droplets ultimately slows and governs the rate at which the size of MDI generated aerosols can shrink to the respirable range.

Because atmospheric air, compressed air, and the air in the lung contain water vapor, the behavior of aqueous aerosols can vary as a function of the environmental humidity. Pure water aerosols will obviously tend to evaporate at all relative humidities less than 100%. At constant temperature, aqueous aerosols containing dissolved salts have a particular relative humidity with which they exist in equilibrium. At this relative humidity, which is roughly predictable from a consideration of Raoult's law and a psychrometric chart,[17] they show no tendency to grow or shrink. However, systems which are isotonic with blood are very dilute and tend to evaporate as they pass in dilution air from a nebulizer to the patient. The opposite occurs with some hypertonic solution and dry powder aerosols.[1] These often display hygroscopic growth in the humid environment of the lung.[1,18] The relative humidity in the lung is in excess of 99% at 37°C.[2] This relative humidity would be that measured over a solution of isotonic saline at the same temperature. Water-soluble drugs administered as hypertonic solutions or solids, therefore, tend to grow rapidly as they pass through the humid environment of the respiratory tract.[18,19] The size they try to attain during inhalation is defined theoretically by the aqueous droplet size which would contain a drug concentration isotonic with blood. These concentrations are often of the order of 1 to 5% showing that the growth tendency of a typical hygroscopic solid is to take on board about 20 to 100 times its own mass of water (employing hypertonic aerosols to enhance deposition in the lung has been advocated recently in the literature[20]). Because the diameter of a droplet is proportional to the cube root of its volume (and ignoring density considerations), a 20-fold growth in mass would correspond to an approximate growth ratio of (equilibrium diameter at lung humidity)/(dry particle diameter) $\approx 20^{1/3}$ or 2.7. In practice during inhalation, ratios less than those predicted at equilibrium are operative because the process is dynamic. Nevertheless, this discussion shows the importance of paying careful attention to the various humidities which can be encountered in administration systems as well as the hygroscopic tendencies of some solid materials.

IV. AEROSOL GENERATION

There are two major types of nonmetered inhalation device which are used largely for the treatment and prevention of respiratory disease. These are jet or ultrasonic nebulizers. In practice, neither of these have been well accepted for the delivery of therapeutic agents for systemic purposes. Systemic administration potential clearly exists, however, given the wide acceptance of this route for the administration of drugs of abuse. Inhalation offers rapid absorption opportunities for compounds which require fast onset. Furthermore, the anatomical arrangements of the major vessels are such that they could usefully be employed to target absorbed compounds to the heart.

Mainly over the last decade, the design and construction of devices has been improved in order to enhance the drug doses which can be delivered successfully to the breathing-impaired. The main improvements have been to increase the output of respirable aerosol. This has been achieved in two ways: first, by increasing total output concentrations and secondly, by reducing droplet or particle sizes emitted by nebulizers. Because of recent improvements in aerosol dust-generator design and the usefulness of these latter devices for animal experimentation and

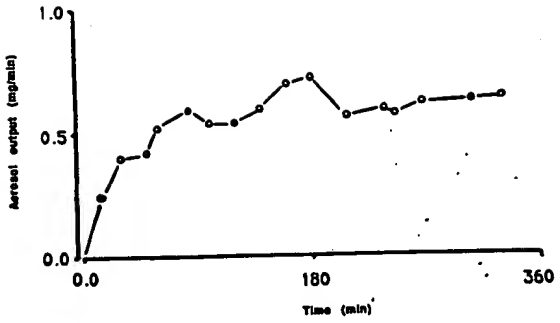

FIGURE 3. Mass of micronized disodium fluorescein powder emitted per minute as dry powder aerosol from a Model 3400 fluidized bed aerosol generator (TSI, St Paul, MN)[14] supplied with dry air at 10 l/min. Aerosol concentrations approach constancy after approximately 3 h when conveyed powder input to the fluid bed is balanced by aerosol ouput from the generator.

toxicity testing, the following discussion includes three major device categories. These are discussed in turn alongside some of the accessories which are commonly used with them: (1) dry powder generators, (2) air-blast nebulizers, and (3) ultrasonic nebulizers.

A. DRY POWDER GENERATORS

Dust generators have long been in existence, the most famous of which is probably the Wright Dust-Feed Apparatus.[21] However, these generators have historically been difficult to adapt to pharmaceutical studies. More recently, fluidized bed technology has improved to such an extent that generators are now available commercially which are capable of deaggregating powder charges and providing these as dispersions of powders in air.[14,22] The dispersed dust can often be shown to possess the same size characteristics as the powder with which the bed was supplied.[22] Thus, it is possible to micronize pharmaceutical powders, pass these into a bed of metal beads which are fluidized by dry air or gas which causes the beads to appear to "boil", and utilize the aerosol formed by the deaggregating action of the bed. Provided the bed is fed with powder continuously, a steady state is reached between powder input and aerosol output which demands that the aerosol output remain at a constant concentration (Figure 3). Steady-state concentrations of respirable aerosol (<5 μm aerodynamic diameter), which can approach 1 mg/l under some circumstances, are several times higher from these devices than those which can be produced by other generators.[14] The high concentrations are important for reasons described below. The devices themselves and their utilization have been described in more detail elsewhere.[14,22] They are manufactured and marketed by TSI (St. Paul, MN).

Performance of inhalation dosimetry and toxicity studies usually requires dose ranging and is often severely limited by the maximum available aerosol concentration emitted by the chosen generator. This is especially true for pharmaceutical studies where it is important that the stability of the administered compound is maintained during aerosol generation. Condensation generators, for example, require vaporization of the chemical agent prior to its condensation as a high concentration aerosol.[23] Such a procedure is usually unacceptable in pharmaceutical trials.[24] The selection of a generator which provides the greatest output concentration is important for two main reasons. First, and most important, respiratory (as opposed to systemic) toxicity is extremely difficult to detect, yet it remains important, even in phase I studies of new

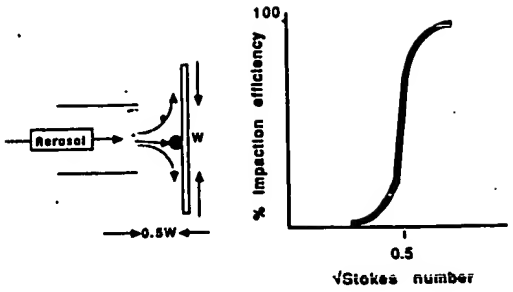

FIGURE 2. Diagrammatic representation of particle impaction as an aerosol stream impinges on a horizontal plate in its path. Impaction efficiency is often approximately 50% when √(Stokes' number) = 0.5.

to the impaction surface is held equal to 1/2 the width of the tube, W, and is thus equal to the maximum distance a particle or droplet traveling down its center must deviate from the airflow in order to collide with the surface in its path. Figure 2 also shows a typical plot of impaction efficiency as a function of the dimensionless Stokes' number, Stk, which, for unit density spheres >1 μm in diameter, in air at 1 atm and 20°C, can be written in the centimeter-gram-second system as:

$$Stk = V\,d^2/(0.00165\,W) \qquad (2)$$

where V is the linear velocity of the airflow and d is droplet diameter. Because √Stk is often ≈0.5 (Stk = 0.25) for a 50% probability of impaction occurring (Figure 2), it is a simple matter to calculate the approximate linear velocity at which a droplet of known diameter will impact in an arrangement like that shown in Figure 2. If, for example, W were 1 cm and d = 5 μm (or 5 × 10^{-4} cm) then the critical velocity for a 50% chance of impaction would be

$$V_{50\%} = \frac{0.25 \times 0.00165 \times 1}{(5 \times 10^{-4})^2} = 1650\ \text{cm/s} \qquad (3)$$

or 16.5 m/s. In order to increase impaction of smaller droplets in this set up, greater velocities are necessary. Alternatively, the value of 0.5 × W (the distance the droplet needs to deviate from the airflow) can be made smaller. Calculations of this type are relevant to baffle design in jet nebulizers and particle deposition from MDIs. They can also be used to explain why impaction is only a major mechanism of deposition in the upper airways of the lung where the linear airflow velocities remain high.

B. SEDIMENTATION

Table 2 shows sedimentation velocities of unit density spheres in still air at 20°C. The values only attain meaning when used in conjunction with aerosol residence times in containers of known dimensions. Consider, for example, an aerosol flowing horizontally at 5 l/min along a 30 cm tube with an internal diameter equal to 2 cm. The linear airflow velocity is given by (volume flow rate)/(area) or (5000 $cm^3\,min^{-1}$)/1 π cm^2 = 1592 cm min^{-1}. The residence time in 30 cm of tubing (30 cm/1592 cm min^{-1} = 0.0188 min) is thus 1.13 s. Because a 10-μm sphere can settle 0.35 cm in this residence time, about 18% of 10 μm spheres will be deposited in the tube during the passage of the aerosol. This percentage is a function of droplet size and can be